

Report of the National Heart, Lung, and Blood Institute Working Group on Research in Adult Congenital Heart Disease

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The Working Group on research in adult congenital heart disease (ACHD) was convened in September 2004 under the sponsorship of National Heart, Lung, and Blood Institute (NHLBI) and the Office of Rare Diseases, National Institutes of Health, Department of Health and Human Services, to make recommendations on research needs. The purpose of the Working Group was to advise the NHLBI on the current state of the science in ACHD and barriers to optimal clinical care, and to make specific recommendations for overcoming those barriers. The members of the Working Group were chosen to provide expert input on a broad range of research issues from both scientific and lay perspectives. The Working Group reviewed data on the epidemiology of ACHD, long-term outcomes of complex cardiovascular malformations, issues in assessing morphology and function with current imaging techniques, surgical and catheter-based interventions, management of related conditions including pregnancy and arrhythmias, quality of life, and informatics. After research and training barriers were discussed, the Working Group recommended outreach and educational programs for adults with congenital heart disease, a network of specialized adult congenital heart disease regional centers, technology development to support advances in imaging and modeling of abnormal structure and function, and a consensus on appropriate training for physicians to provide care for adults with congenital heart disease. (J Am Coll Cardiol 2006;47:701-7) © 2006 by the American College of Cardiology Foundation

In September 2004, the National Heart, Lung, and Blood Institute (NHLBI) and the Office of Rare Diseases, both components of the National Institutes of Health, Department of Health and Human Services, jointly convened a Working Group on research in adult congenital heart disease (ACHD). The purpose of the Working Group was to advise the NHLBI on the current state of the science in ACHD and barriers to optimal clinical care, and to make specific recommendations for overcoming those barriers. The members of the Working Group (listed in the Appendix in the online version of this paper) were chosen to provide expert input on a broad range of research issues

from both scientific and lay perspectives. This report combines an overview of research, training, and educational needs in the field of ACHD with a discussion of the Working Group's recommendations for how to meet those needs.

BACKGROUND

To provide the framework for discussion, participants at the Working Group meeting presented information on various aspects of ACHD. Because issues in the diagnosis and treatment of ACHD are well-reviewed elsewhere (1-5), this

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Abbreviations and Acronyms

ACHD	= adult congenital heart disease
CHD	= congenital heart disease
NHLBI	= National Heart, Lung, and Blood Institute
RV	= right ventricle/ventricular

report focuses primarily on defining the areas of greatest research need.

Congenital heart defects are the most common group of birth defects, occurring in approximately 8 in 1,000 newborns (6). The improvements in diagnostic, interventional, and critical care skills have resulted in survival of approximately 90% of these children to adulthood (7). In 2000, it was estimated that there were 368,800 adults with simple congenital heart disease, 302,500 adults with conditions of moderate complexity, and 117,000 with conditions of great complexity, with a total of 787,800 (8). For the same year, it is estimated that there are 320,000 children with simple conditions, 165,000 with moderately complex conditions, and 138,000 with highly complex conditions, with a total of 623,000 (9).

Now, for the first time in history, these estimates suggest that more adults than children are living with congenital heart disease, and this population is estimated to be growing at 5% per year (10). This growth rate predicts that the total ACHD population in 2005 is likely to have reached one million. It is possible that this figure is low because of the many ACHD patients who are not routinely followed up, a phenomenon likely to underestimate in particular the number of minority patients. Furthermore, whereas in the past it was thought that congenital heart defects seen in adults represented the mild and simple portion of the spectrum, it now seems that the number of adults with conditions of moderate or severe complexity outweighs that of children. This puts a very different face on the requirements for research and education needed to maintain optimal health and prevent secondary disability in this population.

As the past has shown, continuing medical breakthroughs will result in new populations of adult survivors with ever more complex disease. The recipients of the first Norwood procedures (11) and the earliest survivors of arterial switch procedures (12) are now young adults, and their numbers will increase dramatically over the next 10 years. For the first time, adults with single-ventricle physiology represent a significant number of those living with congenital heart defects.

Many of these individuals may not realize that they should be receiving regular care, and even for those who seek care, access may be limited by insurance considerations and by the absence of an adequate cadre of pediatric and adult cardiologists appropriately cross-trained. The limited data available suggest that only a fraction of adult patients with congenital heart disease are followed up by appropriately trained physicians in a setting in which required services are available. Furthermore, there is no universal data

collection program linking the ACHD centers; hence, the opportunity to improve patient outcomes has not been realized. Because the prevention of secondary disability is an important part of ACHD management, this lost opportunity translates into increased human suffering, reduced productivity, and societal cost.

KEY SCIENTIFIC QUESTIONS

The Working Group started with the premise that a systematic approach to the understanding and management of ACHD would best meet the needs of patients. Components of such an approach include identifying and educating patients, providing diagnostic and treatment services, identifying risk factors for adverse outcomes, and expanding the pool of appropriately trained individuals to care for patients with ACHD.

Patient identification and education. A large number of patients with ACHD have no regular cardiology care or are not aware that they could benefit from ongoing care. Only 37% to 47% of patients in the Canadian Adult Congenital Heart Center Consortium have had a successful transition from pediatric cardiology care to adult medicine, and this is a highly structured health system without significant financial access issues (13). Twenty-seven percent of these patients had not had a single evaluation beyond their 18th birthday. In the Natural History Study, 40% of patients with aortic stenosis, pulmonary stenosis, and ventricular septal defect had not had a cardiac examination in more than 10 years (14). In a general population of patients who have not been evaluated and followed up as rigorously as in the Natural History study, this rate is likely to be even higher.

Assessment tools and management issues. Complete assessment of functional status as well as evaluation of abnormal hemodynamic workload in ACHD requires structural and functional imaging data coupled with hemodynamic data. Modeling tools that incorporate anatomic and fluid dynamic information are needed to evaluate complex cardiac anatomy and support patient specific surgical planning. Evaluation of functional status in congenital cardiac malformations requires a multi-modality approach that includes two- and three-dimensional echocardiography, angiography and catheter-based hemodynamic evaluations, computed tomography, and magnetic resonance imaging, as well as the trained technologists and physicians to interpret the tests.

Assessment of the right ventricle (RV), which plays an important role in many types of ACHD, poses particular problems. Many adults with congenital heart disease (CHD) have abnormal RVs because the procedures that had early success, with the most rapid improvement in survival were either operations on patients with two ventricles in which the RV was abnormal (e.g., tetralogy of Fallot) or in conditions in which the RV was the systemic ventricle (e.g., transposition of the great vessels). Current techniques for assessing

left ventricular function are based on well-established mathematical models, which have advanced to include measurement of diastolic as well as systolic function. For the RV, there is still a lack of adequate geometric models in healthy hearts and disease states. The wide variability in geometry and loading conditions of the RV in ACHD makes geometric modeling particularly challenging. Also, limited knowledge of muscle fiber orientation, and heterogeneity of material properties in the postoperative RV in patients with ACHD, have limited the ability to develop realistic models. Nevertheless, such a modeling approach is indispensable for quantitative assessment of RV performance.

Assessment of cardiovascular status in ACHD also requires consideration of ventricular-vascular coupling. The ventricular-arterial system is designed to receive and deliver flow through a balance of forces that preserves energy and minimizes stress relationships between ventricular myocardium, central and peripheral conduits, resistance vessels, and the microvasculature (15–17). Adult patients with CHDs have abnormalities that directly affect key determinants of ventricular-vascular coupling. Specific examples include nonpulsatile systemic venous inflow in single-ventricle palliations (18), impaired atrial-ventricular transport in patients with atrial-level repair for transposition of the great arteries (19), pulmonary endothelial dysfunction seen in pulmonary arterial hypertension and in nonpulsatile systemic venous-pulmonary connections (20), postoperative diastolic dysfunction (21,22), RV outflow aneurysm in patients with tetralogy of Fallot (23), and pulmonary arterial and aortic root enlargement (24).

Changes in intrinsic heart rate, stroke volume, pulse pressure, systemic arterial impedance, neurohormonal or cardiac autonomic nervous system activity, or salt and water control seen in such patients may have substantive effects on health and functional capacity for affected individuals (25–28).

Numerous challenges face the cardiology practitioner when confronted with ACHD patients (29,30). Many patients have sequelae that increase in frequency over time, such as dysrhythmias, sudden death, ventricular and valvular dysfunction, thrombosis, pulmonary hypertension, and endocarditis. Durability of prosthetic materials or pacing therapy is also of concern (31). Syndromes such as Down syndrome are associated with progressive medical problems (32), and superimposition of adult diseases such as systemic hypertension or atherosclerotic vascular disease further modifies the underlying congenital cardiovascular defects. Non-cardiac events, such as pregnancy or surgery on other body systems, require special attention and management.

The management of CHD has evolved through trial and error over the past 60 years. Very different strategies have been used in centers around the world because of a combination of factors, including wide variations in anatomy, the interposition of co-morbidities, the variability in diagnostic modalities, the serendipity of surgical experience, and the availability of support services. As a result, the number of patients in each subgroup is small in the experience of a

single institution. Thus, the remarkable advances in management of CHD have been created through a combination of the occasional radically new management paradigm proposed by individuals or institutions and logical incrementalism, rather than by carefully designed studies. This heterogeneity of management has created a diverse set of issues, even for patients with the same underlying lesion.

Dysrhythmias affect up to 50% of patients with ACHD and include sudden death, ventricular tachycardia, intra-atrial muscle reentry tachycardia/atrial flutter, and bradycardia (33–41). Cardiac pacing is not uncommon in this setting and may include antitachycardia pacing or single- or dual-chamber pacing for rate control. The study of electromechanical coupling requires sophisticated approaches, including simultaneous three-dimensional imaging and mapping. Cardiac pacing and resynchronization offer many valuable new approaches to the management of dyssynchrony and arrhythmia but as yet have not been thoroughly exploited in this population. Newer information about ventricular synchronization and cardiomyopathy have altered the strategies for ventricular pacing, although long-term studies of cardiac pacing and cardiomyopathy in ACHD are lacking (42,43).

Most women with CHD reach childbearing age and wish to become pregnant. Congenital heart disease is now the most common form of heart disease encountered during pregnancy in the U.S. The management of pregnant women with prosthetic heart valves placed to treat CHD is particularly difficult (44,45). Ideal management strategies are difficult to delineate because each center has small numbers of patients and no collaborative multicenter studies have been performed. Because many adults with CHD can now conceive and bear children, and their children are several-fold more likely to have CHD than the general population, this group should undergo genetic evaluation to help predict recurrence risk. Specific genetic mutations may affect the risk and specificity of recurrence, so knowledge of the mutations could help in family counseling.

Identification of risk factors for adverse outcomes. Knowledge of long-term outcomes for adults with complex CHD is necessary to provide optimal care and to guide the refinement of intervention in childhood. The importance of genetics in many facets of medicine has become paramount, and new discoveries in cardiology show the genetic contribution to CHD. Specific genetic malformations may affect outcome, for example, the finding that mutations in the transcription factor *Nkx2.5* not only are associated with structural cardiac malformations, but also may predispose individuals to arrhythmias (46,47). It is reasonable to speculate that individuals with ACHD and this mutation may experience more morbidity than unaffected individuals.

Three congenital malformations commonly encountered in adulthood are tetralogy of Fallot, transposition of the great arteries, and single-ventricle physiology.

TETRALOGY OF FALLOT. Tetralogy of Fallot is the most common complex defect with the longest surgical history and the greatest documentation of outcomes. Long-term postoperative residua include RV outflow tract obstruction or aneurysm, pulmonary regurgitation, distal pulmonary artery obstruction, atrial and ventricular incisional scars, residual or recurrent ventricular septal defects, myocardial hypertrophy, chamber enlargement, RV and left ventricular dysfunction, aortic root dilation, and aortic regurgitation (48–51). The three most common late causes of death are arrhythmia, heart failure, and complications of reoperation (52). Pulmonary regurgitation, far from being benign as initially thought, has emerged as a principal reason for late reoperation. There is no consensus on the optimal timing of pulmonary valve replacement. In addition, the RV outflow tract reconstruction may affect cardiac autonomic nervous activity, which may in turn affect exercise hemodynamics via heart rate recovery, respiratory physiology, and a decreased systolic blood pressure response with reduced cardiac output reserve (53).

Long-term survival after complete intracardiac repair is 86% at 32 years (52). However, the risk of sudden cardiac death increases in a time-dependent fashion, and by 30 years after surgery, is approximately 6% to 9% (54). The etiology of sudden death is multifactorial; identified risk factors include QRS duration ≥ 180 ms, older age at repair, significant pulmonary valve regurgitation (55), with potential for prognostic categorization via electrophysiologic testing. As noted earlier, these factors may change as patients from later surgical eras reach adulthood. Furthermore, there is increasing evidence that chronic pulmonary regurgitation leads to progressive RV dilation and dysfunction, requiring intervention to recover performance. Management of this patient group remains controversial with respect to timing of intervention and whether associated procedures impact on long-term outcomes (56).

COMPLETE OR D-TRANSPOSITION OF THE GREAT ARTERIES.

Complete or d-transposition of the great arteries was uniformly lethal until the advent of the atrial switch procedures (Mustard, Senning). However, these procedures opened up a Pandora's box of long-term problems, including failure of the systemic RV, baffle leaks and obstruction, pulmonary hypertension, and dysrhythmias (48).

For the past two decades, the arterial switch operation (ASO) has been the treatment of choice for patients with transposition of the great arteries; midterm follow-up has confirmed good systemic ventricular function and lack of arrhythmias. This can be contrasted with the known long-term increased mortality and morbidity with atrial switch procedures. However, long-term concerns after the arterial switch operation include coronary insufficiency, myocardial ischemia, ventricular dysfunction and arrhythmias, and issues regarding stenoses at the great arterial anastomotic sites as well as development of aortic and pulmonary dilation and regurgitation (57). In the series reported by Formigari

et al. (58), 35% had neo-aortic regurgitation (native pulmonary valve), particularly after two to four years postoperatively, although most cases were mild and patients remained stable without progression over the follow-up period (median) of 8.2 years. Losay et al. (57) reported on 1,200 patients with ASO for transposition of the great arteries between 1982 and 1999 with prospective follow-up of 1,095 survivors. Freedom from reoperation was 82% at 15 years, with the most frequent cause being pulmonary stenosis, primarily at the anastomotic site, and was most frequent within the first nine postoperative years. Moderate or greater pulmonary stenosis was observed in 3.9%, including those who had surgical repair or balloon dilation. Aortic regurgitation of all grades was seen in 15.5%; aortic regurgitation of grade II or higher was observed in 3.8% with an increase in frequency over time. Survival was 88% at 10 and 15 years; hazard function for death declined rapidly, with no deaths after 5 years. Late mortality was related to reintervention or major events in the intensive care units. Good left ventricular function in sinus rhythm was generally maintained.

SINGLE-VENTRICLE PHYSIOLOGY. Single-ventricle physiology comprises several types of cardiovascular malformation, such as hypoplasia of the left or right ventricle, atresia of one of the atrioventricular valves, double-inlet ventricles, or undifferentiated single ventricles. Although collectively single ventricle is a rare defect, present only in 1.5% of patients with CHD (59), it accounts for a disproportionate share of morbidity and mortality in ACHD. The usual surgical approach for single-ventricle physiology culminates in the Fontan procedure, which separates the systemic and pulmonary circulations. Cyanosis is thus eliminated, but the systemic circulation often is supported by the single RV, which is ill-designed for this purpose as indicated by the known late failures of the systemic RV. Reported outcomes depend on the age of the patient at operation, the precise anatomy, and any previous palliative procedures, as well as the era of operation and the current modifications relative to the experience and techniques of the specific institution. Issues that compromise quality of life include protein-losing enteropathy, thromboembolic complications, ventricular dysfunction, and dysrhythmias both early and late after the Fontan procedure (60–62). Cardiorespiratory and ventilatory responses to exercise after the Fontan procedure are subnormal, including lower-than-expected $\text{VO}_{2\text{max}}$, cardiac output, and heart rate responses, as well as an abnormal reduction of normal resting arterial O_2 saturation at peak exercise (63). Pre-adolescents who undergo volume-unloading surgery at an early age have better aerobic capacity than those whose surgery is at a later age (64). This is partially because of the morphology of the systemic ventricle, duration of volume loading and cyanosis, and degree of atrioventricular valve regurgitation before the Fontan procedure. Diastolic filling abnormalities are common regardless of ventricular morphology. They may exist

without RV hypertrophy in patients with RV morphology (65). Even in long-term Fontan procedure survivors, there is often reduced systolic ventricular function despite normal ventricular mass and volume. This may be caused by the absence of the normal interaction between two ventricles, mediated by the interventricular septum, resulting in marked differences in myocardial twist and strain (66).

Training. The 32nd Bethesda Conference entitled "Care of the Adult With Congenital Heart Disease" addressed the issue of workforce description and educational requirements for the care of adults with CHD. The Task Force emphasized the shortage of trained adult cardiologists and the difficult transition from the pediatric cardiologist to a medical cardiologist for the care of patients with complex CHD. The Bethesda Conference report outlined three levels of training from basic exposure to CHD patients to higher levels of specialization. The requirements for ACHD providers were outlined in detail, and the report indicated that the time required for the training of future ACHD cardiologists should be determined by a Special Task Force of the American Board of Internal Medicine and the American Board of Pediatrics.

There are many parallels with the status of training of specialists for ACHD with that of pediatric cardiology in the 1960s. During that era, there were never more than one or two pediatric cardiologists in any large center, and the vast majority of major hospitals in the United States did not have specialists in this area. The advent of clinical training grants resulted in the training of sufficient personnel to bring to the bedside the tremendous progress that was being made in the diagnosis and treatment of pediatric heart disease. Not only was there an immediate effect, but this governmental effort propagated further advances in clinical care and research that provided direct and indirect funding for a critical mass of specialists. The circumstances are similar today for ACHD. Rarely does a major medical center have more than one or two individuals devoted to this specialty, and most general cardiologists do not have specific expertise. In many ways, that crisis in ACHD is even greater than for pediatric cardiology in the 1960s in that there are more patients who require care, and they will require care for a much longer period of time. The superimposition of acquired heart disease during middle and older adult life further complicates their management.

Fortunately, the number and types of training and research grants have grown since the 1960s. ACHD centers are eligible to apply for institutional training grants (T32s), and a full panoply of individual fellowships, career development awards, and research grants is available for professionals interested in ACHD, just as for other areas of interest.

RECOMMENDATIONS

The specific recommendations developed by the NHLBI Working Group are summarized below, and are meant to complement recommendations made by the ACC Bethesda

Conference 32 and other groups working on these important issues:

- Outreach programs should be established to identify the "lost" population of adults with CHD. This effort should be conducted in conjunction with medical centers, schools of public health, government offices, and patient groups.
- A network of specialized ACHD regional centers should be formed. The purposes of this network would be to:
 - develop a database that would be used to track outcomes, formulate best practices, and foster continuous quality improvement based on these best practices.
 - develop a rich environment suitable for training and continuing education of cardiologists in ACHD as clinicians, researchers, and educators.
 - design and conduct multi-center clinical research on the pressing clinical issues in ACHD. These include but are not limited to natural history of specific conditions, interaction of ACHD with adult cardiovascular risk factors, assessment and treatment of ventricular dysfunction, understanding of ventricular-vascular interactions and their role in circulatory failure, predictors of risk for sudden death and serious arrhythmias, understanding of genetic factors influencing outcome, and improved pregnancy management.
- Technology should be developed to support hemodynamic and functional modeling of individual patients, to improve understanding of cardiac status, and to plan for future therapy. This will require:
 - improvements in imaging systems, image processing and image display;
 - development of near-real-time mechanical models for surgical planning; and
 - engineering solutions to support these activities.
- A consensus on training is required, and the NHLBI Working Group strongly endorses the recommendations of the 32nd Bethesda Conference on training. New approaches to training ACHD specialists require:
 - cooperative efforts by the American Board of Internal Medicine, the American Board of Pediatrics, the NHLBI, and others to facilitate the entry of physicians with medical or medical/pediatric training into the field of ACHD.
 - funding for both clinical and research training to produce adequate numbers of physicians to provide care for this large cohort of patients.
 - current training programs working with NHLBI to determine appropriate mechanisms to support training of ACHD specialists.

SUMMARY

Congenital heart disease is arguably one of the most complex and variable disease states. Management of CHD in the pediatric population has only recently been subjected to systematic study with the establishment of the NHLBI-

funded Pediatric Heart Network. Systematic study has been effective in reducing mortality and morbidity in other conditions such as heart failure, cystic fibrosis, and pediatric cancers. We propose a similar collaborative, multi-disciplinary approach for the adult patient with CHD. The heterogeneity of these lesions, although adding to the difficulty of study, provides important models for the understanding of basic embryology, genetics, and physiology with clear extrapolations to acquired cardiac and noncardiac pathology. Therefore, in addition to enhancing the quality of life and functionality of this patient group, there will be benefits for the whole of society.

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APPENDIX

For a list of the Working Group members and federal participants, please see the online version of this article.